Seizure 1998; 7: 159–162

Cognitive effects of anticonvulsant monotherapy in elderly patients: a placebo-controlled study

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Old age is recognized to be the commonest time in life to develop epilepsy. There is a perception that older patients are more sensitive to the deleterious cognitive effects of antiepileptic drugs (AEDs). Elderly patients (median age 70 years, range 60–88 years) taking anticonvulsant monotherapy (10 carbamazepine [CBZ], 8 sodium valproate [VPA], 5 phenytoin [PHT]) took an extra dose of their usual medication (200mg CBZ, 500mg VPA, 100mg PHT) and matched placebo each for a month in random order. The concentrations of AEDs were higher after 7 and 28 days of active treatment compared with placebo (7 days: CBZ 9.5 vs. 7.8 mg L^{-1}, $p < 0.05$; VPA 97 vs. 64 mg L^{-1}, $p < 0.05$; PHT 13 vs. 11 mg L^{-1}, $p < 0.05$; 28 days: CBZ 9.4 vs. 7.7 mg L^{-1}; $p < 0.01$, VPA 85 vs. 60 mg L^{-1}, $p < 0.05$; PHT 16 vs. 13 mg L^{-1}, $p < 0.05$). Despite these increases in concentration, there were no significant changes in attention, reaction time, finger tapping, memory, side-effect scale or sedation scoring during the active phases compared with placebo phases for the three drugs analysed together and separately. Elderly patients taking standard AEDs as monotherapy did not develop cognitive impairment when the dose was modestly increased within the target range for each drug.

Key words: anticonvulsants; epilepsy; elderly; cognitive function.

INTRODUCTION

Epilepsy is a major cause of morbidity in the elderly[1]. Several studies have shown that there is an age-related increase in it prevalence, resulting in epilepsy ranking as the third commonest neurological disorder (after stroke and dementia) in patients over 60 years of age[2,3]. Factors associated with the development of a seizure disorder in this population include the increasing likelihood of cerebrovascular disease, cerebral tumours and metabolic/toxic events[4]. With the expanding elderly population, the number of older patients having epilepsy can be expected to rise[5]. There are few studies exploring AED efficacy and toxicity in the elderly[6,7]. As a result, dosing schedules are based on the results of trials in younger patients. Treatment involves balancing optimal seizure control against susceptibility to adverse effects taking into consideration concomitant disease, drug interactions and the physiological changes associated with ageing that result in altered pharmacokinetics and pharmacodynamics[8].

The potential for deleterious effects of AEDs on cognitive function in the elderly is of particular importance. The incidence and severity of cognitive impairment rises sharply with age. In younger patients, there has been a plethora of studies exploring the relationship of seizures, AEDs, underlying pathology with cognition[9–11]. Polypharmacy has been recognized as increasing the likelihood of impairment, as does, not surprisingly, higher doses and plasma concentrations of AEDs[12–17]. Early studies supported the hypothesis that individual AEDs varied in their propensity to cause cognitive adverse effects, but more recent research suggests that, at equivalent serum concentrations, phenobarbital, phenytoin (PHT), carbamazepine (CBZ), oxcarbazepine and valproic acid (VPA) can all produce cognitive impairment to a similar extent[10]. Different cognitive modalities can, however, be affected by different AEDs[18]. Fewer studies have compared the cognitive consequences of increased doses of AEDs[19–21]. We have sought to examine the cognitive abilities of elderly patients with epilepsy, before, during and after an increase in their monotherapy doses of CBZ, VPA or PHT using a double-blind, placebo-controlled design.

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1059-1311/98/020159 + 04 $12.00/0

Table 1: Mean [SEM] antiepileptic drug concentrations (ranges) at each time period during adjunctive active and placebo treatment.

	Carbamazepine			Sodium valproate			Phenytoin		
Visit	*n*	Active	Placebo	*n*	Active	Placebo	*n*	Active	Placebo
Baseline	10	7.6 [0.5] (6.1–11)	7.7 [0.4] (5.7–9.1)	8	63 [6.1] (39–87)	65 [7.6] (35–85)	5	9.9 [1.6] (3.4–12)	12 [1.3] (9.9–16)
Day 1	10	8.5 [0.5] (7.2–11)	7.5 [0.4] (6.6–9.9)	8	71 [7.6] (62–85)	62 [7.6] (36–82)	5	10 [1.4] (5–14)	12 [1.6] (9.2–18)
Day 7	10	9.5* [0.5] (7.7–12)	7.8 [0.5] (6.1–9.7)	8	97* [5.5] (72–112)	64 [9.1] (35–76)	5	13* [0.9] (11–16)	11 [1.1] (8–15)
Day 28	10	9.4** [0.3] (8.1–11)	7.7 [0.6] (6.2–10)	8	85* [10] (47–123)	60 [9.0] (46–86)	5	16* [1.7] (12–21)	13 [1.8] (9.3–18)

All results are expressed in mg L^{-1}.
* $p < 0.05$.
** $p < 0.01$.

METHODS

Patients

Twenty-three patients (11 female, 12 male) with a mean age of 70 years (range 60–88 years) were recruited from the epilepsy clinic at the Western Infirmary in Glasgow. All were receiving stable regimens of CBZ, VPA or PHT as monotherapy with no change in dosing over the preceding three months. Seventeen patients had a mean (range) seizure frequency of one (1–10) per month in the three months prior to the study, with six patients being seizure-free during this period. All recruited patients completed the study. Patients were required to score more than 7 on the MEAMS dementia screening test to ensure participation. The study had the approval of the Western Ethical Committee and all patients gave written informed consent.

Protocol

At the initial visit, patients completed a self-assessment questionnaire providing details of their epilepsy and its treatment. Seizure frequency and descriptions were recorded on standard seizure charts. Each underwent a battery of cognitive function tests. A 20 ml blood sample was withdrawn for AED concentrations. Patients were randomized to receive either an extra dose of their usual medication (200 mg CBZ, 500 mg VPA, 100 mg PHT) or matched placebo in a double-blind fashion for 28 days. After a 2-week washout period, they were transferred to the alternative treatment for a further 4 weeks. Patients were monitored on days 1, 7 and 28 of both study periods. On each occasion, blood was withdrawn for anticonvulsant assay and the cognitive function test battery was repeated at the same time since dosing on each occasion. At the final visit, seizure charts were reviewed. Patients were asked which treatment they preferred. Those who benefited from an increased dose of their medication remained on it.

Cognitive function testing

A standard battery of cognitive function tests was performed as detailed by Gillham *et al*[20]. These tests have been widely employed in a range of previously published studies investigating the cognitive effects of AEDs[15–22]. A brief summary of the individual tests is given below.

Intelligence. Verbal IQ was calculated from the score on the National Adult Reading Test. Performance IQ was measured by a standard method using the score on Raven's standard progressive matrices.

Threshold detection. Each patient was shown a variety of rectangles on a visual display unit. After a very short period of time, an additional rectangle appeared on the screen. The 'threshold' was the minimum time period from the presentation of the rectangle display and the appearance of the additional rectangle, which the patient required to identify its presence.

Choice reaction time. This test was based on the choice reaction time facility of the Leeds psychomotor tester. It was defined as the time taken in milliseconds to move the index finger from a base marker and

Table 2: Selected mean (SEM) reaction, memory, attention and symptomatology scores before and after 28 days of both treatments.

	Reaction	Memory			Attention	Symptomatology	
	Choice reaction decision time (ms)	Digit span forward	Visual span backward	Word-pair learning	Threshold task (frame units)	Concentration	Mood
CBZ—baseline	0.6 (0.1)	6.6 (0.4)	2.9 (0.4)	10 (1.8)	1.9 (0.4)	3.2 (1.1)	1.2 (0.7)
CBZ—placebo	0.6 (0.1)	6.4 (0.5)	3.0 (0.2)	11 (1.1)	1.6 (0.5)	2.6 (1.0)	1.5 (0.9)
CBZ—active	0.6 (0.1)	6.4 (0.5)	4.7 (1.5)	7.4 (1.7)	1.8 (0.5)	3.5 (1.0)	1.5 (0.9)
VPA—baseline	0.6 (0.04)	5.5 (0.3)	2.9 (0.3)	12 (1.9)	3.1 (0.6)	2.7 (1.1)	0.7 (0.4)
VPA–placebo	0.6 (0.03)	6.3 (0.4)	3.3 (0.3)	11 (2.3)	3.5 (0.9)	3.9 (1.0)	0.6 (0.6)
VPA—active	0.8 (0.1)	5.9 (0.5)	2.9 (0.3)	12 (1.7)	3.4 (0.5)	3.2 (0.6)	1.2 (0.8)
PHT—baseline	0.6 (0.1)	6.8 (0.4)	4.0 (0.3)	9 (2.4)	2.2 (0.3)	2.2 (1.6)	3.6 (2.2)
PHT—placebo	0.6 (0.1)	7.4 (0.5)	3.4 (0.3)	13 (2.8)	2.1 (0.3)	3.0 (1.5)	2.6 (1.1)
PHT—active	0.6 (0.1)	6.4 (0.4)	3.6 (0.4)	10 (1.7)	2.4 (0.5)	2.5 (1.1)	4.3 (1.9)

extinguish a light in response to its appearance at one of six target markers. The decision time was the time taken to respond to the light coming on by removing the finger from the base button. The mean of 30 trials was recorded for both.

Finger tapping. This involved counting the number of taps/min achieved by the dominant index finger on a calculator button in constant addition mode. A series of practice runs was allowed before final scoring.

Digit span. Patients first recalled a maximum number of digits in ascending order following an oral presentation. This process was then repeated with digits in a reverse order. The patient was allowed two trials at each level and the task was discontinued when both were failed.

Visual span. Patients were presented with a series of words which they were asked to recall, initially in order of presentation (forward span) and subsequently in reverse order (backward span). They were allowed two trials at each level, and the task was discontinued when both were failed.

Word-pair learning. This involved counting the number of trials which each patient required to reach the target of three correct pairings when associating unrelated words.

Symptomatology. Questionnaires were completed requesting details on possible AED adverse effects of headache, dizziness, itch, diplopia, ataxia, dry mouth, breathlessness, nausea and palpitations. These symptoms were rated 'none, mild, moderate or severe'. Subjective scores of sedation, memory, concentration and mood were obtained on 10 cm visual analogue scales.

Analysis

Blood samples were taken into heparinized tubes, centrifuged immediately and the plasma stored at −20 °C for batch analysis. CBZ, VPA and PHT concentrations were obtained by enzyme immunoassay (EMIT, Syva, Palo Alto, USA). AED concentrations were compared using students' two-sample t-test. Multivariant statistical analysis was performed for the cognitive function tests using MINITAB for Windows statistical package (Version 10.1) on a Viglen 4DX266 microcomputer.

RESULTS

Twelve patients received active treatment first with 11 taking placebo. Plasma AED levels were statistically significantly higher during the active treatment phases at days 7 and 28 compared with the placebo treatment phases (Table 1). Seizure frequency (mean±SEM) was better on the active treatment month for all three drugs (CBZ: active 0.5 ± 0.34, placebo 0.6 ± 0.4; VPA: active 0 ± 0, placebo 0.38 ± 0.38; PHT: active 0.2 ± 0.2; placebo 2.2 ± 1.9). Only five patients subsequently stayed on the increased dose of their medication (3 CBZ, 1 VPA, 1 PHT). No significant change was observed in any cognitive test comparing active treatment with placebo at any time point for the three drugs analysed together and separately. Selected results are shown in Table 2. A complete data set can be obtained on request from the authors.

DISCUSSION

It can be anticipated that as the incidence of epilepsy in the elderly continues to rise, the potential dele-

terious effects of AEDs will assume increasing importance[23]. It is generally held that cognitive function in the elderly is particularly susceptible to the adverse effects of AEDs[9]. During this small double-blind randomized study, we were able to achieve clinically and statistically relevant increases in AED plasma levels with patients taking a modest extra dose of CBZ, VPA or PHT during the active treatment phase. Despite concentrations often in the upper reaches of the relevant target ranges for the drugs[24], we found no significant alteration in cognitive function when comparing active with placebo treatments both overall and for each individual drug. Patients with poorly controlled epilepsy were not included to avoid the potential confounding factor of seizure activity.

In a recent survey of prescribing practice of UK geriatricians, CBZ and PHT were most often prescribed first, with VPA largely second choice[25]. We have previously demonstrated in younger patients that VPA has little significant impact on cognitive function in therapeutic dosage, but found that CBZ tended to adversely influence psychomotor activity and PHT memory[18]. More recently, however, Craig and Tallis[6] reported that VPA and PHT had little effect on cognitive function in older people. Older patients taking standard AEDs do not necessarily develop cognitive impairment when the dose of their medication is modestly increased within the target ranges for the drugs. Further studies are required with both the newer and established AEDs in this vulnerable population of patients.

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